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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/465,133	12/15/1999	ELISABETTA VEGETO	246/180	8491

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EXAMINER	
QIAN, CELINE X	
ART UNIT	**PAPER NUMBER**
1636	17

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/465,133	Applicant(s) VEGETO ET AL.	
	Examiner Celine X Qian	Art Unit 1636	

-- The MAILING DATE of this communication app ars on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *100-105,107,108,111-123,127 and 129-197* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *100-105,107,108,111-123,127 and 129-197* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/15/99* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 100-105, 107, 108, 111-123, 127, 129-197 are pending in the application.

This Office Action is in response to the Amendment filed on 12/24/02.

Response to Amendment

The rejection of claims 118, 119, 136, 137, 139, 141-143 under 35 U.S.C. 112 second paragraph has been withdrawn in light of Applicants' amendment of the claims.

The rejection of claims 100-105, 107, 108, 111-123, 127 and 129-143 under 35 U.S.C.112 first paragraph (written description) is maintained for reasons set forth of the record mailed on 6/12/02 and further discussed below.

The rejection of claims 100-105, 107, 108, 111-123, 127 and 129-143 under 35 U.S.C.112 first paragraph (scope of enablement) is maintained for reasons set forth of the record mailed on 6/12/02 and further discussed below.

Claims 100-105, 107, 108, 111-123, 127, 129-197 are rejected under 35 U.S.C 101 for reasons discussed below.

Claims 144-168 are rejected under 35 U.S.C. 112 first paragraph (written description) for reasons discussed below.

Claims 144-197 are rejected under 35 U.S.C. 112 first paragraph (scope of enablement) for reasons discussed below.

Claims 111 and 168-176 are rejected under 35 U.S.C. 112 second paragraph for reasons discussed below.

Response to Arguments

Claims 100-105, 107, 108, 111-123, 127 and 129-143 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In response to the written description rejection, Applicants argue that the specification has provided relevant identifying characteristics of the claimed mutated steroid hormone superfamily ligand binding domain in the specification by teaching the ligand binding domain of the non-mutated steroid hormone superfamily ligand binding domain, mutation in this region, and the chemical properties of the mutated ligand binding domain, for example, its ability to distinguish a steroid hormone receptor antagonist and agonist. Thus, the structural and functional relationship is present because mutation of the C-terminal domain of the receptor results in altered affinity and function of the ligands. Applicants further argue that the specification has provided a specific example that a mutated progesterone receptor having a deletion of 42 or 54 amino acids from the C-terminus is capable of binding a natural antagonist of the wild type receptor. Applicants argue this example is sufficient to represent the entire claimed genus as in case of In re Herschler.

These arguments have been fully considered but deemed unpersuasive for following reasons. The claimed genus is "mutated steroid hormone receptor binding domain" which encompasses any and all mutations to all steroid superfamily receptor ligand binding domains that are capable binding an antagonist (of the natural occurring binding domain) and causes transcription of the responsive gene. The above teaching does not sufficiently describe this

genus because it does teach which mutation(s) within the C-terminus of the 300 amino acid is responsible for the observed function. The specification also fails to teach mutation(s) in other steroid receptor ligand binding domain would result in the same function. Therefore, the specification neither describes a representative number of species of the invention by their complete structure nor other relevant identifying characteristic. Thus, the written description requirement is not met.

The application of case law In re Herschler is not proper in this case because the claimed steroids are in different context. In fact, the reason that the disclosure of corticosteroid is sufficient to support the claims drawn to a physiologically active steroid is because their chemical property of being carried through a layer of skin by DMSO is quite similar. It stated, "Steroids, when considered as drugs, have a broad scope of physiological activity. On the other hand, steroids, when considered as a class of compounds carried through a layer of skin by DMSO, appear on this record to be chemically quite similar. The diversity of exemplified materials "potentiated" by DMSO in the great-grandparent application, is much broader than the diversity of steroid compounds shown contemporaneously in the art. In this instance, we conclude that one having ordinary skill in this art would have found the use of the subgenus of steroids to be apparent in the written description of the great-grandparent application. Were this application drawn to novel "steroidal agents," a different question would be posed." The case law also states that "written description of class of compounds must provide measure of predictability for utility described for that class." In this case, the description provided by the specification must provide measure of predictability of whether any and all mutations within 300 C terminus amino acid of all the steroid receptor superfamily ligand binding domain can result in

its function of distinguishing natural or modified ligands. The instant specification fails to do that because it only provides a single example of deletion of 42 or 54 amino acid of progesterone receptor that result in such function. Therefore, the specification fails to describe the invention in such a way to convey one skilled in the art that the inventors had possession of the invention at the time the application was filed.

Claims 100-105, 107, 108, 111-123, 127 and 129-143 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In response to the enablement rejection, Applicants argue that the specification has provided adequate teaching (regarding level of expression of transgene in a transgenic animal, mutated steroid hormone receptor superfamily ligand binding domain and transgenic animals for long term expression) for the enablement of the claimed invention so that undue experimentation is not necessary to carry out the method.

The above arguments have been fully considered but deemed unpersuasive. The method of regulating gene expression *in vivo* as claimed encompasses the use of transgenic animal comprising a construct encoding the mutant receptor and another construct encoding the responsive element to the receptor and a reporter gene. However, as indicated in the previous Office action, it is unpredictable whether the transgene would be expressed at a level sufficient to cause a particular phenotype (see page 8-9 of the previous action for details). In other words, it is unpredictable whether the transgene would be expressed at a high enough level so that it can

be detected, and thereby, the expression can be regulated. One skilled in the art would not know how to use transgenic animals that simply comprise the transgene without actual mRNA or protein expression to practice the method as claimed. The specification has taught how to make such transgenic animals and how to detected gene expression. However, the specification does not teach a method overcome the unpredictability to make transgenic animals with predicted "phenotype" that is necessary for claimed method (discussed in the office action mailed on 8/29/01). The specification does not teach how to use such a transgenic animal without a phenotype. Therefore, one skilled in the art would have to engage in undue experimentation to practice the method as claimed.

In regard to the argument toward "mutated steroid hormone receptor superfamily ligand binding domain," the Examiner considers the teaching of specification is not sufficient for the enablement of any and all such mutated binding domain for its function as a molecular switch. As discussed in the previous office action and above, a single example of deletion of 42 C-terminus amino acid from the progesterone receptor cannot extend the predictability of its function in other members of the receptor family or other types of mutation of the receptors. The teaching of the structure of the wild type receptor that 300 amino acid is responsible for binding of ligand is not sufficient to support the notion that any mutation within this region would make it a molecular switch as claimed. In fact, the specification teaches that it is difficult in distinguishing among amino acid residues that affect the overall structure of this domain from those directly involved in a direct contact with the ligand because this binding domain folds into a complex tertiary structure. Therefore, whether any mutation in this region in any steroid

receptor would result in a molecular switch as claimed is unpredictable. Therefore, one skill in the art would have to engage in undue experimentation to practice the method as claimed.

In regard to the argument that long term expression can be achieved, the Examiner considers the teaching of the specification is not sufficient for the enablement of the method claimed. Integration of exogenous DNA into chromosome by non viral vector is a low frequency event which requires selection to detect the expression of exogenous DNA. Viral vectors such as adenoviral vector or AAV are not known to integrate into host chromosome. Even for retroviral vector, it also has the problem of sustaining long term expression at high level (see discussion on page 10 of the office action mailed on 8/29/01). Therefore, the method is not enabled for long term expression.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 100-105, 107, 108, 111-123, 127, 129-197 are rejected under 35 U.S.C. 101 because they are not directed to statutory subject matter. It is PTO policy not to issue claims that encompass humans (see 1077 OG 24, April 21, 1987). This rejection may be overcome by inserting "non-human" before "animal".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 144-168 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (see the reasons discussed in the response to argument section and previous two office actions).

Claims 144-197 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of regulating gene expression transiently *in vivo* by either a) introducing into a wild type animal a construct encoding a progesterone receptor with at least 42 amino acid deletion from C-terminal, and another construct comprising a progesterone receptor responsive element linked to a report gene; b) administering a ligand that binds to said mutated receptor to said animal, or administering a ligand that binds to a mutated steroid receptor to a transgenic non-human animal, wherein said transgenic non-human animal expresses a heterologous reporter gene and a mutated steroid receptor, wherein expression of said receptor regulates the expression of the reporter gene by binding to the promoter of said reporter gene, does not reasonably provide enablement for said method utilizing any transgenic animal or long term expression in any animal, and/or any mutated steroid hormone receptor that is capable of binding ligand that is an antagonist of the natural occurring receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims (see the reasons discussed in the response to argument section and previous two office actions).

Claims 111, 168-176 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 111, Applicants stated that the claim is amended to overcome the previously raised rejection. However, no such amendment was found in the response. Therefore, the rejection is maintained.

Regarding claims 168-175, the term "molecule switch expression cassette" renders the claim indefinite because it is unclear what this term encompasses. It appears that it refers to a molecular switch expression cassette. Applicants are advised to clarify this matter.

Claim 176 recites the limitation "transient expression" in line 1. There is insufficient antecedent basis for this limitation in the claim because claim 135 does not have this limitation.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
March 10, 2003

REMY YUCEL, PH.D
SUPERVISORY PATENT EXAMINER
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